HIGH PRODUCTION VOLUME (HPV)

CHEMICAL CHALLENGE PROGRAM

TEST PLAN

For

2,4-DICHLOROPHENOL, SODIUM SALT

Prepared by:

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PLAIN ENGLISH SUMMARY

This test plan addresses 2,4-dichlorophenol, sodium salt (CAS No. 3757-76-4). Existing data are summarized. No additional data will be collected under the HPV Challenge Program.

EXECUTIVE SUMMARY

The Dow Chemical Company hereby submits for review and public comment the test plan for 2,4-dichlorophenol, sodium salt, under the Environmental Protection Agency's (EPA) High Production Volume (HPV) Chemical Challenge Program. It is the intent of The Dow Chemical Company to use new information in conjunction with a variety of existing data and scientific judgment/analyses to adequately characterize the SIDS (Screening Information Data Set) human health, environmental fate and effects, and physicochemical endpoints for this chemical.

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I. INTRODUCTION

The Dow Chemical Company has committed voluntarily to develop screening level human health effects, environmental effects and fate, and physicochemical test data for 2,4-dichlorophenol, sodium salt under the Environmental Protection Agency's (EPA's) High Production Volume (HPV) Challenge Program (Program).

This plan identifies the chemical and its CAS number, identifies existing data of adequate quality for the chemical, and outlines testing planned to develop screening level data for the chemical under the Program. The objective of this effort is to identify and develop sufficient test data and/or other information to adequately characterize the human health and environmental fate for the chemical in compliance with the EPA HPV Program. Physicochemical data that are requested in this program will be provided.

II. DESCRIPTION OF 2,4-DICHLOROPHENOL, SODIUM SALT

A. The Chemical

2,4-dichlorophenol, sodium salt (CAS No. 3757-76-4) is used in the production of pesticides. This material has been studied to provide safe handling information.

III. TEST PLAN RATIONALE

A. Classification of the Chemical as a Production Chemical

1. Requirements

Classification of 2,4-dichlorophenol, sodium salt is as a production chemical under the EPA HPV program.

2. Toxicological Equivalency of 2,4-Dichlorophenol and the Sodium Salt of 2,4-Dichlorophenol

The OECD "Guidance for the Use of Structure-Activity Relationships (SAR) in the HPV Chemicals Programme" includes the opportunity to use SAR for health endpoints. The goal is to find toxicity data for an analog that can be used to address the testing needs of an HPV chemical and thus, reduce testing.

Valid analogs should have close structural similarity. Examples in the guidance document of surrogate data to characterize individual chemicals are as follows:

1) ***"Chemicals that are essentially the same in vivo. For example, different salts of the same anion or cation. The salts must fully dissociate in vivo and the counter ion must not contribute any more (or less) toxicity.***

2) *A chemical that metabolises to one (or more) compounds that have been tested. The metabolism must be rapid and complete."*

3) *Chemicals that have only minor structural differences that are not expected to have an impact on toxicity. All functional groups must be the same."*

Appendix B of the OECD "Guidance for the Use of Structure-Activity Relationships (SAR) in the HPV Chemicals Programme" provides examples from OECD SIDS cases and includes a specific example of acid-salt pairs (chloroacetic acid/sodium salt). In the case of the acid-salt pairs, no testing was considered necessary because the combined data for the acid/salt pair covered all of the SIDS endpoints. Similar to the SIDS approach for chloroacetic acid/sodium salt, the potential health effects of Na-DCP are adequately represented by the toxicological data for DCP based on the following physical-chemical data and SAR.

Although there does not appear to be any specific mammalian toxicological data available for the sodium salt of 2,4-dichlorophenol (Na-DCP), one would expect that Na-DCP would be toxicologically equivalent to 2,4-dichlorophenol (DCP) on a molar basis. The water solubility of DCP is 4 g/L at (25 degrees C) and the water solubility for Na-DCP is 7.05 g/L (20 degrees C, pH 7). The dissociation constant (pKa) for Na-DCP is 7.8, which is the same as DCP. Thus, Na-DCP would be expected to quickly dissociate to sodium and DCP in an aqueous environment such as the mammalian body. Upon the dissociation of Na-DCP, sodium would not be a significant factor in the metabolism or toxicity of DCP and thus, the systemic toxicity of Na-DCP would be equivalent to DCP on a molar basis. Therefore, the mammalian toxicological data for DCP are adequate for the evaluation of the potential hazards of the sodium salt of DCP.

Strong support for the predicted toxicological equivalency of DCP and Na-DCP is demonstrated in the extensive toxicological data base of the closely related molecule 2,4-dichlorophenoxyacetic acid (2,4-D) and its salts and esters. Numerous regulatory studies have been conducted with 2,4-D acid as well as the diethanolamine, dimethylamine, isopropylamine and triisopropanolamine salts and the butoxyethylhexyl and 2-ethylhexyl esters (Munro *et al.*, 1992; Kennepohl and Munro, 2001). A very extensive and complete toxicological database is available for 2,4-D acid. Toxicological studies with the amines and esters include pharmacokinetic, acute, subchronic dietary, 21-day dermal, developmental and genetic toxicity studies.

A joint meeting of the FAO Panel of Experts on Pesticide Residues and the WHO Expert Group on

Pesticide Residues (JMPR) has reviewed the extensive toxicological data for 2,4-D and its salts and esters (JMPR, 1997). These experts concluded "…that the toxicities of the salts and esters of 2,4-D were comparable to that of the acid." The basis for this conclusion is detailed in the following information abstracted from the Meeting's report:

"Pharmacokinetic studies with salts and esters of 2,4-D have shown that the salts dissociate and the esters are rapidly hydrolysed to 2,4-D. The similarity in the fate of 2,4-D and its salts and esters explains their similar toxicities.

"After dermal applications of 2,4-D to volunteers, 5.8% of the dose was absorbed within 120 h. When the acid and its dimethylamine (DMA) salt were applied, 4.5% of the acid and 1.8% of the salt were absorbed, and of this 85% of the acid and 77% of the salt were recovered in the urine 96 h after application.

"In six studies of toxicity rats fed diets containing the diethanolamine (DEA), [dimethylamine] DMA, isopropylamine (IPA), or tri-isopropanolamine (TIPA) salt or the butoxyethylhexyl (BEH) or 2-ethylhexyl (EH) ester at acid-equivalent doses of 0, 1, 15, 100, or 300 mg/kg bw per day for 13 weeks, the results demonstrated the comparable toxicity of the acid, salts and esters. The NOAEL was 15 mg acid equivalent per kg bw per day for all six compounds.

"Dogs were given gelatin capsules containing 2,4-D at 0, 0.3, 1, 3, or 10 mg/kg bw per day or diets containing 2,4-D, the DMA salt, or the EH ester at acid-equivalent doses of 0, 0.5, 1, 3.8, or 7.5 mg/kg bw per day for 13 weeks. Treatment-related findings were observed in the three studies at 3 mg/kg bw per day and above. The NOAEL was 1 mg acid equivalent per kg bw per day in all three studies.

"The developmental toxicity of the DEA, DMA, IPA, and TIPA salts and the BEH and EH esters was evaluated in pregnant rats after oral administration during days 6-15 of gestation. The acid-equivalent doses were 11, 55, or 110 mg/kg bw per day for the DEA salt; 12, 50, or 100 mg/kg bw per day for the DMA salt; 9, 25, 0r 74 mg/kg bw per day for the IPA salt; 12, 37, or 120 mg/kg bw per day for the TIPA salt; 17, 50, or 120 mg/kg bw per day for the BEH ester; and 10, 30, or 90 mg/kg bw per day for the EH ester. The maternal and developmental toxicities of the salts and esters of 2,4-D were comparable to those of the acid…The overall NOAELs were approximately 10 mg acid equivalent per kg bw per day for maternal toxicity and 50 mg acid equivalent per kg bw per day for developmental toxicity. [Developmental toxicity studies in pregnant rabbits with the same compounds resulted in similar findings.]

"In order to evaluate the dermal toxicity of 2,4-D and its salts and esters, rabbits received 15 dermal applications of the acid, the DEA, DMA, IPA, or TIPA salt or the BEH or EH ester at acid-equivalent doses of 0, 10, 100, or 1000 mg/kg bw per day for 6 h per day on

five days per week for 21 days. No systemic toxicity was observed at any dose, and no dermal toxicity [dermal lesion] was observed with the acid, the TIPA salt, or the BEH ester. Dermal lesions were observed in rabbits treated with the DEA, DMA, or IPA salt, or the EH ester at 100 mg/kg bw per day and above. The [dermal] lesions were characterized as acanthosis, hyperkeratosis, oedma, inflammation, and epidermal hyperplasia. The NOAEL was 10 mg acid equivalent per kg bw per day for dermal toxicity and 1000 mg acid equivalent per kg bw per day (the highest dose tested) for systemic toxicity."

The single-dose oral LD_{50} values for 2,4-D acid, esters (isooctyl, isobutyl, butoxyethanol and butyl), and salts (dimethylamine and sodium) ranged from 553 mg/kg (isobutyl ester in female rats) to 1090 mg/kg (dimethylamine salt in male rats) (Gorzinski *et al*., 1987). The LD_{50} values for the acid, esters, or salts, when expressed as acid equivalents, were consistent which suggests that the acute oral toxicity was due to 2,4-D per se. The acute dermal LD_{50} values in rabbits for 2,4-D acid, esters, and salts also were similar in that they generally were greater than 2000 mg/kg.

The acute dermal LD_{50} for DCP is 780 mg/kg bw in Sprague-Dawley rats. This value is based on a study that utilized test substance that was melted at 40° C in order to obtain the liquid form of the test material and more closely mimic accidental exposures. The potential for systemic toxicity or lethality from dermal exposure obviously is dependent upon a combination of the dermal absorption potential of a compound as well as its inherit systemic toxicity. Since DCP and dissociated Na-DCP would be expected to have equivalent systemic toxicity on a molar basis, differences in the systemic toxicity from dermal exposure of these compounds would be determined primarily by differences in dermal penetration.

Na-DCP has significantly less potential for systemic toxicity due to dermal exposure than DCP based on a comparison of physical-chemical properties as well as quantitative structure-permeability relationships (QSPRs) for percutaneous absorption. The partition coefficient (K_{ow}) for DCP is in the range of 2.92-3.25 (3.1 used for subsequent calculations) while the partition coefficient for Na-DCP is estimated at 0.12 (a lower K_{ow} would be expected for a salt which has higher water solubility). Molecular size (molecular weight) and hydrophobicity (as the logarithm of the octanol-water partition coefficient; Log K_{ow}) are the primary determinants of transdermal penetration (Moss *et al.*, 2002). Hydrophilic compounds have low skin permeability and hydrophobic compounds have high skin permeability; different Log K_{ow}-dependent QSARs can be used to predict skin permeability. High molecular weight compounds (>150 Dalton) with Log K_{ow} <0.5, such as Na-DCP, are in a category with the lowest permeability coefficient (K_p). On the other hand, high molecular weight compounds with 0.5 Log K_{ow} 3.5, such as DCP, have larger K_p values. Calculation of K_p values according to the equation of Cronin *et al*. (1999) [Log K_p = 0.77 log K_{ow} - 0.0103 MW - 2.33] results in a K_p ratio >300 for DCP:Na-DCP. QSPR analysis demonstrates that Na-DCP has significantly less potential for dermal absorption than DCP and thus, less potential for acute dermal toxicity than DCP.

The physical chemical properties of Na-DCP and DCP not only are the basis for expected differences in potential dermal toxicity, these properties also appear to be important in the recommendations for

immediate decontamination after dermal exposure. Reports of worker fatality cases from exposure to relatively small amounts of molten DCP prompted the U.S. Government to issue an advisory and notice of potential risk (EPA OPPT and OSHA, 2000). The advisory refers to research that indicates that octanol-water partition coefficients are indicative of lipophilicity which often correlates strongly with toxicity and skin penetration (Lopez *et al*., 1998). The researchers studied two homologous series, phenyl alcohols and p-alkylanilines, and found that the optimal lipohilicity for skin penetration, expressed as log P (n-octanol), was 3.1 which is very similar to the value for DCP. The advisory suggests that flushing skin exposed to DCP with an alkaline solution (soap, sodium bicarbonate, sodium carbonate, etc.) would convert the DCP to its ionized (salt) form, which would be more rapidly dissolved. The advisory goes on to state that a secondary benefit of an alkaline solution is that the ionized form of DCP would be much less lipophilic and, therefore, less readily absorbed into the skin. Thus, these recommendations are consistent with the conclusion of our QSPR analysis that indicated Na-DCP would have much less potential for dermal penetration and toxicity than DCP.

As prescribed by the OECD "Guidance for the Use of Structure-Activity Relationships (SAR) in the HPV Chemicals Programme," the above evaluation of the physical-chemical data and SAR indicate that the potential health effects of Na-DCP are adequately represented by the toxicological data for DCP. Utilization of the same classification, labeling and handling precautions for Na-DCP as for DCP would be conservative and clearly protective for human health even though no specific data are available for Na-DCP.

B. Human Health Effects

There are six mammalian toxicity endpoints in the HPV Program:

- Acute Toxicity
- Repeated Dose Toxicity
- Genetic Toxicity *In Vitro*
- Genetic Toxicity *In Vivo*
- Reproductive Toxicity
- Developmental Toxicity

Published and unpublished data for 2,4-dichlorophenol, as detailed in the attached Robust Summaries, satisfy the requirements of all required mammalian testing. We propose that no further testing is necessary. The attached Robust Summaries with the proposed testing provide adequate data to characterize the human health effects endpoints under the Program.

C. Ecotoxicity

There are three aquatic toxicity endpoints in the HPV Program:

- Acute Toxicity to Fish
- Acute Toxicity to Aquatic Invertebrates
- Toxicity to Algae (Growth Inhibition)

EPA identifies the following test methods to determine these endpoints: OECD Guideline 203, *Fish Acute Toxicity Test*; Guideline 202, *Daphnia sp., Acute Immobilization Test*; and Guideline 201, *Alga Growth Inhibition Test* [2] or equivalent studies.

Published and unpublished data for 2,4-dichlorophenol and its sodium salt, as detailed in the attached Robust Summaries, satisfies requirements for ecotoxicity data.

The existing data, along with the proposed testing, will be adequate to characterize ecotoxicity endpoints under the Program.

D. Environmental Fate

Predictive models as well as laboratory assays were used to develop meaningful data for 2,4-dichlorophenol. The environmental fate data include:

- Photodegradation
- Stability in Water (Hydrolysis)
- Transport and Distribution (Fugacity)
- Biodegradation

1. Photodegradation

Photodegradation was measured in laboratory testing, as detailed in the attached Robust Summaries.

2. Stability in Water (Hydrolysis Modeling)

Hydrolysis of an organic chemical is the transformation process in which a water molecule or hydroxide ion reacts to form a new carbon-oxygen bond. Chemicals that have a potential to hydrolyze include alkyl halides, amides, carbamates, carboxylic acid esters and lactones, epoxides, phosphate esters, and sulfonic acid esters [3]. Stability in water was measured experimentally, as detailed in the attached Robust Summaries.

3. Chemical Transport and Distribution In The Environment (Fugacity Modeling)

Fugacity based multimedia modeling can provide basic information on the relative distribution of chemicals between selected environmental compartments (i.e., air, soil, sediment, suspended sediment, water, biota). The US EPA has acknowledged that computer modeling techniques are an appropriate approach to estimating chemical partitioning (fugacity is a calculated endpoint and is not measured). A widely used fugacity model is the EQC (Equilibrium Criterion) model [6]. EPA cites the use of this model in its document titled *Determining the Adequacy of Existing Data*, which was prepared as guidance for the HPV Program.

In its document, EPA states that it accepts Level I fugacity data as an estimate of chemical distribution values. The input data required to run a Level I model include basic physicochemical parameters; distribution is calculated as percent partitioned to 6 compartments within a unit world. Level I data are basic partitioning data that allow for comparisons between chemicals and indicate the compartment(s) to which a chemical is likely to partition.

The EQC Level I is a steady state, equilibrium model that utilizes the input of basic chemical properties including molecular weight, vapor pressure, and water solubility to calculate distribution within a standardized regional environment. This model will be used to calculate distribution values for 2,4-dichlorophenol. A computer model, EPIWIN - version 3.02, will be used to calculate the properties needed to run the Level I EQC model.

4. Biodegradation Testing

Biodegradation is the utilization of a chemical by microorganisms as a source of energy and carbon. The parent chemical is broken down to simpler, smaller chemicals, which are ultimately converted to an inorganic form such as carbon dioxide, nitrate, sulfate, and water. Assessing the biodegradability of organic chemicals using a standard testing guideline can provide useful information for evaluating chemical hazard.

Biodegradation values for 2,4-dichlorophenol, sodium salt, as detailed in the attached Robust Summaries, were experimentally determined.

E. Physicochemical Properties

The physicochemical properties include:

- Melting Point
- Boiling Point
- Water solubility
- Octanol/Water Partition Coefficient

Data for physicochemical properties are summarized and detailed in the attached Robust Summaries.

IV. TEST PLAN SUMMARY

The following testing, modeling, and technical discussions will be developed for 2,4-dichlorophenol and thus for 2,4-dichlorophenol, sodium salt:

- Calculate fugacity data.

Summaries of results will be developed once the data are available. This test plan is expected to provide adequate data to characterize the human health effects and environmental fate and effects endpoints under the Program.

For reasons indicated in the above paragraphs, we do not believe additional data needs to be generated beyond the studies listed. Due to the nature of the chemical; the manner in which the chemical is manufactured, distributed, processed and used, the product stewardship measures taken to prevent exposure; and existing human/environmental data, we believe that our workers, the public and the environment are well protected from exposure to the material.

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